J Orthop Spine Trauma. 2020 March; 6(1): 1-8. DOI: http://dx.doi.org/10.18502/jost.v6i1.4534

Review Article

An Introduction to Tissue Engineering and Orthopedic Applications

Fatemeh Baghaie Nia[1], Fatemeh Khavari[1], Masoumeh Firouzi[2], Mohammad Hossein Nabian[3,*]

[1] Medical Student, Department of Orthopedics, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
[2] Assistant Professor, Research Center for Neural Repair (RCNR), University of Tehran, Tehran, Iran
[3] Assistant Professor, Department of Orthopedic Surgery, Shariati Hospital, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

[*] Corresponding author: Mohammad Hossein Nabian; Center of Orthopedic Trans-Disciplinary Applied Research (COTAR), Tehran University of Medical Sciences, Tehran, Iran. Tel: +98-9126305095, Email: dr.nabian@gmail.com

Received: 20 October 2019; **Revised:** 17 January 2019; **Accepted:** 04 February 2020

Abstract

Nowadays, orthopedic-related pathologic conditions are considered as a growing concern. Also, the conventional treatments (grafting techniques) are not efficacious enough for the growing clinical needs. In the last decades, researches have been focused on finding more effective alternative treatments. Tissue engineering (TE) is a newly emerging field of science that has great potential to reduce these clinical issues. There are three main components in TE including cells, biomaterials, and signals. Choosing the best combination of these components is a vital decision in a TE process. In this review article, we are going to discuss TE and its components and also highlight some of the researches in the field of orthopedic TE by focusing on some tissues including bone, cartilage, skin, skeletal muscle, peripheral nervous system (PNS), tendon, and ligament. In the end, TE, as a new field of science, faces some major challenges that we will address some of them in this article.

Keywords: Tissue Engineering; Orthopedic; Cell Engineering; Bioengineering; Tissue Therapy

Citation: Baghaie Nia F, Khavari F, Firouzi M, Nabian MH. **An Introduction to Tissue Engineering and Orthopedic Applications.** *J Orthop Spine Trauma* 2020; 6(1): 1-8.

Background

Complete restoration of damaged tissues and organs has always been the dream of mankind (1). Regenerative medicine (RM) is a multidisciplinary field of health sciences that aims to retrieve normal biological function and structure of tissues damaged by acute or chronic diseases, trauma, aging, congenital defects, etc. To reach this goal, RM benefits from various specialties such as tissue engineering (TE), biomaterials, cell biology, and cloning (2-6). The "Tissue Engineering" term was probably coined for the first time by Robert Nerem in the second half of the 20th century (7). It was described as use of techniques and rules of engineering and life sciences towards the achievement of a basic understanding of functional/structural correlations in the normal and abnormal physiological condition in mammalian tissues. One major aim in TE is developing biological substitutes that restore, maintain, or improve damaged tissues and their functions (7). In this narrative review, we are going to focus on TE disciplines and their applications in orthopedics.

TE Components

Although TE consists of multifarious elements depending on different strategies, there are three major components that are needed for fabrication of artificial tissues. This "triad of TE" includes biomaterials, cells, and signals (Figure 1) (8-10).

Biomaterials: Biomaterial or scaffold is a 3-dimensional (3D) structure that acts as an extracellular matrix (ECM) in a normal functional tissue. Biomaterial constructions should be cytocompatible and degradable to reduce unwanted host responses. Beside accurate size and shape, a proper biomaterial should possess appropriate functional, physical, and mechanical features to act as a structural support for the fabricated tissue and promote tissue growth (9, 11, 12).

They provide adhesion sites for transport of cells or bioactive molecules such as adhesion peptides or growth factors. The most common types of biomaterial classes are natural biomaterials (e.g., collagen) and synthetic polymers [e.g., poly (glycolic acid) (PGA)] (3).

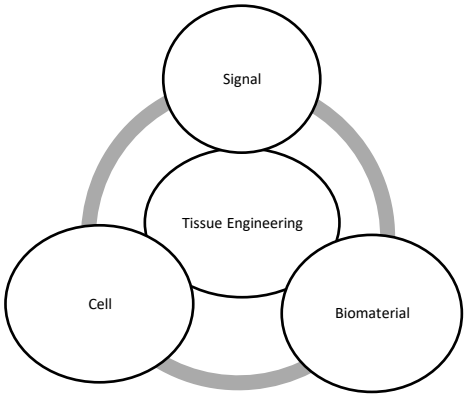

Figure 1. Triad of tissue engineering (TE)

Cells: The human body builds up countless number of heterogeneous cells (10). The production of appropriate cell line is an essential part of TE which leads to functional tissue and organs. These cells are used to regenerate, heal, or improve the function of tissues by manufacturing factors, signals, and other molecules like ECM components (9, 11). Two main groups of cells are used in TE: mature differentiated cells (e.g., fibroblast cells) and stem cells [e.g., embryonic stem cells (ESCs) or adult stem cells] (11). Also, based on the harvesting source, they are classified as autograft, allograft, or xenograft (13).

Signals: In physiological environment, the "signals" are agents of collaboration, coordination, and harmony. The signals can rearrange the genetic expression of target cells to proliferation, differentiation, ECM production, or many other functions (9, 10). There are four subgroups of signals: biological, chemical, mechanical, and electrical. Two important biological signals, growth factors, and cytokines are fundamental for regenerative strategies of TE (12).

TE Applications in Orthopedics

Orthopedic surgeons have always been in search of useful approaches to replace damaged or lost tissues. Many mechanical devices and grafting techniques have been used from past to present (14). Although these methods are successful to certain degree in saving lives and reducing morbidities, they are not always optimal (15). Some of the limitations that current therapies may have are post-surgical complications (e.g., infection), limitation of graft materials and donor site morbidity, risk of rejection in allografts, and the necessity of carrying a mechanical device for a long time (14). The objective of researches in the fields of TE and RM is to reduce post-surgical problems, improve patient's recovery, and eliminate the need for following surgeries or interventions (16). In this part, we review some of the applications of TE techniques in orthopedics.

Bone: Bone as the hardest connective tissue has a high potency of regeneration and repair (9, 17). Nowadays, there has been a dramatic increase in the incidence of bone diseases, particularly in the population affected by obesity, poor physical activity, and ageing (18). One of the challenges in treating bone disorders is nonunion defects. When the defect size exceeds the critical value, the bone tissue loses the ability to repair and requires intervention (19). The gold standard therapy in nonunion is bone grafting (20). Therefore, the research on artificial substitutes of grafting materials is constantly developing, which consequently results in novel treatments for existing diseases (21). The basic idea of bone TE is to understand the correlation of TE components to regenerate functional bone tissue and repair damaged tissues (18, 22, 23).

The scope of this review article is to highlight some of the clinical studies in this field. In a clinical trial by Hernigou et al. in 2009, injection of autologous bone marrow concentration for treatment of osteonecrosis of the femoral head (ONFH) significantly increased the amount of progenitor cells and improved the prognosis (24, 25). In another study performed by Goel et al., percutaneous injection of autologous bone marrow to 20 patients resulted in improvement or healing of tibial nonunion in 15 patients (25, 26). A number of studies in this field demonstrate that polytherapy in TE (i.e., using cells, scaffolds, and signals together) is more effective than single therapy (12). Also, osteoconductive scaffold has led to better results in clinical trials compared to a signal/factor (12).

Extracorporeal shockwave therapy (ESWT) is an effective non-invasive method for treating ONFH, especially in early stage. Evidence shows that this therapeutic strategy improves bone quality by increasing vascularization, vascular endothelial growth factor (VEGF), and nitric oxide. This method was more beneficial compared to the previous therapies like bone grafting or core decompression (27).

In an attempt to utilize new therapy for nonunion and segmental bone defects, Miller et al. conducted a clinical trial on 10 men and 6 women. They used reamer-irrigator-aspirator (RIA) bone grafting enhanced with dexamethasone, a synthetic steroid that can experimentally help mesenchymal stem cells (MSCs) to differentiate into osteoblast during cell culture. Three patients received bone morphogenetic protein (BMP) in addition to RIA and dexamethasone. After a mean of 8 months follow-up, almost all radiographic images showed healing. Analysis gave a mean 6.28 score of 10 in modified Lane and Sandhu scoring system; additionally, two patients got 9 and 10 score (28).

Cartilage: In the field of cartilage regeneration, orthopedic research has been generally focused on articular cartilage injuries and its related disabilities, mainly due to osteoarthritis (OA), rheumatoid arthritis (RA), psoriatic arthritis, degenerative diseases, and trauma (29). Cartilage is a low-cellular non-vascularized connective tissue. The poor capacity of cartilage healing by itself is a result of the absence of adequate vascularity. Cartilage diseases lead to long-lasting disabilities with a constantly growing burden on the health care system (30).

The available pharmacological treatments with palliative intent can only reduce the pain (31). The surgical approaches like arthroplasty for end-stage disease may not completely improve the disability. Also, none of the approaches can successfully restore natural hyaline structure of the cartilage tissue (32). Previous investigations have tried to retrieve chondral function by filling the defect and relieving the pain (30). Despite numerous research efforts, the natural healing process of cartilage tissue is still unknown (33). The novel strategies and therapies aim to decrease the need for joint replacement and increase the quality of life (17).

The available TE clinical strategies in this field are: 1) bone marrow stimulation and augmentation, 2) autografts and allografts, and 3) cell-based techniques (34).

In bone marrow stimulation and augmentation, producing perforations in subchondral plate leads to the formation of blood clot which conducts the recruitment of stem cells and promotes healing (34). However, the main structure of fibrin clot is collagen type 1 and the structure is not biomechanically proportionate for long-term use of cartilage (34, 35). Osteochondral autografts and allografts, as mature viable hyaline cartilage-bone units have been used to fill small cartilage defects. Limitation of the donor site in autograft and type equalizing into the correct shape and architecture in allograft are the most important drawbacks of these methods (34).

Cell-based therapy has been recently noticed (29). The first approach of cell-based therapy, autologous chondrocyte implantation (ACI), was first introduced in 1994, which is the only cell-based therapy approved by the Food and Drug Administration (FDA) (29, 36). This strategy needs two surgeries: first surgery to harvest healthy chondrocytes and second surgery to implant the cultured cells (34). One disadvantage of ACI that could lead to further operation is hypertrophy of tissue (36). MSCs are multipotent cells with self-replication potency that can reduce inflammatory factors and immune responses (29). MSCs application in the early stages of OA has shown excellent results (37). The bone marrow MSCs (BM-MSCs) have more chondrogenic and osteogenic ability compared to other sources (29).

In 2016, Chang et al. showed that patients under 45 years responded better to ACI, in despite of the fact that BM-MSCs are not distinct in different ages (38). In a

randomized control trial (RCT) in 2015, 30 patients with the diagnosis of the knee OA were divided into two groups. The first group (15 patients) received an intraarticular injection of allogeneic BM-MSCs and the second group (15 patients) received only hyaluronic acid (HA). After 12 months, the first group had superior functional and structural improvement in comparison with the control group (37, 39).

Skin: Skin is the outermost part that covers the human body and is at risk of injuries more than any other organ (40-42). Deep injuries (e.g., full-thickness skin wounds) (41) and some metabolic disorders [e.g., diabetes mellitus (DM) and venous insufficiency] may lead to the formation of chronic non-healing wounds that require therapeutic intervention (43). The current gold standard for treating extensive skin wounds is autograft (44). Due to the limitations of grafting, producing artificial skin by TE can be a good substitute (41). There is a list of commercially available skin substitutes that can be categorized as dermal, epidermal, and dermo-epidermal (45).

Epidermal substitutes were first introduced by Rheinwald and Green. They successfully cultured human keratinocytes as a cell sheet (46). Nowadays, these cell sheets are known as cultured epithelial autografts (CEAs) (45). CEAs are not suitable to be used in the reconstruction of full-thickness skin wounds, and also, they do not provide a good dermal-epidermal connection (41).

Integra was one of the first FDA-approved dermal substitutes for treating extensive large burn wounds. Later, it got approval for burn scar reconstruction (47, 48) and some diabetic foot ulcers (47). Integra has a two-layered acellular structure made of a porous bovine collagen and shark chondroitin-6-sulfate, covered with a silicone sheet on top (47, 48). When used in clinical trials, it showed lower infection rate and better outcomes in comparison to conventional treatments (48).

Another approach is using naturally available scaffolds such as amniotic membrane (AM), either alone or as a delivery system for seeded cells. In a recent double-blind phase 1 RCT, Momeni et al. studied the healing of donor sites in 10 burn patients with total burn surface area (TBSA) of 10 to 55 percent. They treated harvested area with Vaseline gauze (control group), AM (AM group), or AM as a delivery system for seeded fetal fibroblasts (AM-F group). Wound closure happened at 10.1 ± 2.4 and 11.3 ± 2.9 days post-treatment in AM-F and AM groups, respectively. This was significantly shorter compared with the control group (14.8 ± 1.6 days) (49).

Peripheral Nervous System (PNS): PNS is a highly advanced complex network of nerves (50) that can be damaged during different conditions (e.g., motor vehicle accidents, tumor growth, etc.) (51). PNS injuries can cause notable impairment and morbidity (52). In axonotmesis and neurotmesis types of injury, Wallerian degeneration happens in the distal part, and neurotmesis may need a nerve graft (53).

Microsurgery is currently the gold standard technique for nerve repair, which is used to restore the nerve continuity with creation of an anastomosis between proximal and distal stumps (54). For nerve gaps more than 2 cm, nerve grafting is needed (50). Autologous nerve grafting, as the standard method, has some significant limitations and a total successful recovery rate post-treatment of about 50% (50, 55). A probable alternative to the autologous graft is tissue-engineered nerve guide conduits (NGCs).

NGCs are tubular structures made of natural or synthetic polymers that bridge the nerve gap and act as a guidance pathway, providing both structural and trophic support for axon sprouts to pass from proximal to distal end (50, 51). NGCs can be simple empty tubular structures or can be filled with trophic factors or supporting/stem cells which enhance the efficacy and improve axonal regeneration (51, 56). A novel technique is filling the nerve conduit with platelet-rich plasma (PRP) that has shown good results in multiple studies (57-59). This suggests that PRP contains factors (e.g., neurotrophic factors) that improve nerve regeneration (56).

In a prospective RCT performed by Boeckstyns et al., the clinical outcome of conventional treatment (neurorrhaphy) was compared with tissue-engineered collagen conduits in treatment of an injured mixed sensory-motor nerve. There was no significant difference between two approaches in clinical outcome 24 months after repair (60). However, using nerve conduits eliminated the limitations of autograft.

Hou et al. in a recent work done in 2019, used a poly (lactic-co-glycolic acid) (PLGA) NGC filled with intraluminal sponge fillers (known as ISF-NGC) to bridge a 10mm gap in rat sciatic nerve. The ISF-NGC was compared with a hollow PLGA NGC (H-NGC). They observed that structural regeneration and functional recovery were higher in the ISF-NGC group and the findings were comparable with the current gold standard (autograft) (61).

Skeletal Muscle: As one of the most abundant tissues in the human body that form about 40% to 45% of the body weight (62), skeletal muscle has a highly organized structure with a notable ability for spontaneous regeneration (63). Some congenital or acquired conditions can impair this regeneration capacity (e.g., congenital myopathies, large muscle volume loss following traumatic injuries, muscular atrophies, muscle dystrophies, tumor excision injuries, etc.), which have steadily raised with population aging and life expectancy increased in recent decades (64, 65).

Conventional methods are limited for treatment of volumetric muscle loss (VML), a condition defined as losing the volume of muscular mass permanently that can cause functional disorders and cosmetic deficits (66). These methods are mainly based on surgical interventions with common grafting complications. Other treatment methods are mostly rehabilitation options including using mechanical devices (e.g., ventilator devices) or drugs than can replace the missing metabolites (62, 67). For a successful treatment of systemic muscle diseases such as muscular dystrophies, multiple administrations of drugs and missing metabolites and designing a proper delivery system for them are required (68). The basic idea of skeletal muscle TE is generation of new muscle fibers that can be helpful in treatment of such conditions without grafting-related issues (69).

Some of the main approaches in the field of muscle TE are: 1) acellular scaffolds that may promote muscle regeneration, 2) cellular scaffolds that are significantly more effective than previous, 3) engineered muscle grafts derived from cell sheets: although containing high-density cell populations, they lack structural support due to the absence of a scaffold, 4) minced muscle grafts that need in vitro expansion or large harvesting sites, and 5) tissue-engineered muscle grafts (TEMGs) that have a special regeneration capacity with very time-consuming production process. All these methods can be combined with growth or trophic factors to achieve a better clinical

outcome (70).

Successful case of treatment with TE technique was first reported in a 19-year-old marine by Mase et al. in 2010. They replaced the injured quadriceps muscle of a patient suffering from VML injury by a decellularized matrix from small intestine submucosa. The result was promising and new tissue formation was visible on computed tomography (CT) scan at 36 weeks after treatment (71).

In a recent animal study by Wang et al., 18 mice with a 5mm rectus femoris defect were divided into three groups: 1) untreated, 2) treated by a collagen scaffold, and 3) treated by a collagen scaffold seeded with muscle-derived stem cells. The third group had a significant improvement in muscle regeneration compared to others (72).

Tendon and Ligament: Tendons and ligaments are fibrous connective tissues that the main proportion of their dry weight consists of collagen (73). They have a week self-healing ability and cannot completely regenerate after a full-thickness trauma (73, 74), which makes them a good target for TE researches. Tendons and ligaments such as anterior cruciate ligament (ACL) and rotator cuff commonly get injured after trauma or orthopedic surgeries (73-75). The currently available therapies like surgical repair are not durable enough and have a higher failure rate in long term (75).

The TE treatments for tendon/ligament injuries are divided into three main categories: 1) injectable gels for drug delivery, 2) tissue grafts, and 3) synthetic degradable or non-degradable materials (76). However, the number of clinical trials in this field is limited. In two ongoing clinical studies, cell therapy was used to repair a ruptured rotator cuff tendon. In one study, autologous stromal vascular fraction (SVF) cells and in the other one MSCs were injected to supraspinatus muscle and tendon, but the results of researches are not available yet (77).

In another report by Wang et al., the long-term profit of autologous tenocytes in human tendon repair was discussed (78). The patients who participated in this study were suffering from chronic resistant lateral epicondylitis and have not been responsive to non-surgical treatment. After receiving autologous tenocyte injection, they were followed up for about 12 months. According to visual analogue score (VAS), the healing was significant and optimistically durable up to 5 years (75).

Some of the commonly-used cells, biomaterials, and signals in the field of orthopedic TE have been collected in table 1.

Challenges

As a new field of medical science, TE has been continuously developing in recent years, altering the outlook of diseases and respective therapeutic strategies. Correspondingly, it has faced various challenges which can be categorized in four main groups: 1) fundamental challenges, 2) knowledge limitation, 3) evaluation challenges, and 4) clinical challenges (18, 94) (Figure 2).

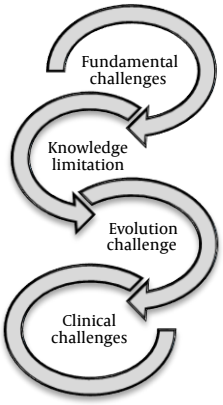

Figure 2. The most common challenges in tissue engineering (TE) can be categorized into four classes, fundamental challenges, knowledge limitations, evolution challenges, and clinical challenges.

Some of the fundamental challenges are selecting capable cells, obtaining an appropriate cell source, and procuring biomaterials to afford a proper scaffold, especially in orthopedic TE that should have considered mechanical and other physical features (95, 96). About signal component, beside the challenges regarding to the selecting an appropriate source, finding optimal time and dosage is another obstacle (97). In large structures such as bone, providing the appropriate vascularization and microenvironment vascularity is also a challenge (95, 98). The limitation of knowledge is a result of small number of TE techniques and slow advancement of clinical and laboratory studies (94). Evaluation difficulties are rooted in lack of sufficient clinical studies, small patient number, the absence of randomization, and lack of control group (12). The clinical challenges include infection (most common), technical restriction, difficulties of approval process, and the absence of a widespread public clinical access (12, 99).

Table 1. The most common components used in different tissue engineering (TE) methods

Tissue	Cell	Biomaterial	Signal
Bone	BM-MSCs, umbilical vein stem cell, AD-MSCs (81, 82)	Collagen, chitosan, PGA, PLA (20, 80)	FGF, TGF-β, PDGF, IGF (79)
Cartilage	Fibroblasts, chondrocytes, adult MSCs, AD-MSCs, BM-MSCs (84, 85)	Cell-derived-ECM (83)	TGF-β and BMP-2 (79)
Skin	Fibroblasts, keratinocytes, MSCs, ESCs, amniotic fluid stem cells, iPSCs (89, 90, 91)	Collagen, chitosan, fibrin, gelatin, elastin, HA, silk, PLA, PGA, polyurethane (42, 87, 88)	VEGF, SDF-1α, FGF (86)
Peripheral nerve	Human umbilical cord MSCs, AD-SCs (51)	Laminin, collagen, elastin, HA, fibrinogen, PLLA, PCL, PLGA (50, 51)	NGF, FGF, NT-3, BDNF, PDGF (92)
Skeletal muscle	Satellite cells, perivascular stem cells, MSCs, and ESCs (70)	Collagen, fibrin, gelatin, HA, chitosan, keratin, alginate, decellularized matrix, PLLA, PLGA, and PCL (63)	HGF, FGF, IGF, VEGF, TGF, NGF (66)
Tendon/ligament	ESCs, fibroblast, MSCs (17, 74)	Proteoglycan, glycoprotein, fibronectin, and thrombospondin (93)	FGF, PDGF-BB, EGF, TGF-β, and IGF (93)

BM-MSCs: Bone marrow mesenchymal stem cells; AD-MSCs: Adipose-derived mesenchymal stem cells; MSCs: Mesenchymal stem cells; ESCs: Embryonic stem cells; iPSCs: Induced pluripotent stem cells; PGA: Poly(glycolic acid); PLA: Polylactic acid; ECM: Extracellular matrix; HA: Hyaluronic acid; PLLA: Poly-L-lactic acid; PCL: Poly(ε-caprolactone); PLGA: Polylactic-co-glycolic acid; FGF: Fibroblast growth factor; TGF: Transforming growth factor; TGF-β Transforming growth factor beta; PDGF: Platelet-derived growth factor; IGF: Insulin-like growth factor; BMP-2: Bone morphogenetic protein 2; VEGF: Vascular endothelial growth factor; SDF-1α Stromal cell-derived factor 1 alpha; NGF: Nerve growth factor; BDNF: Brain-derived neurotrophic factor; NT-3: Neurotrophic factor 3; HGF: Hepatocyte growth factor; EGF: Epidermal growth factor

Conclusion

This narrative review aimed to explain the general concept of TE as a new field of science and its applications in orthopedic surgery. Many researchers in this field are trying worldwide to find novel solutions for emerging orthopedic-related disabilities and conditions by using "triad of TE" and other components. Although there have been some satisfaction, there is still a long way ahead and TE, as well as orthopedic TE, are new emerging fields of science at their young age and more researches need to be done to translate these techniques into the clinical application.

Conflict of Interest

The authors declare no conflict of interest in this study.

Acknowledgments

None.

References

1. Han F, Wang J, Ding L, Hu Y, Li W, Yuan Z, et al. Tissue engineering and regenerative medicine: achievements, future, and sustainability in Asia. *Front Bioeng Biotechnol*. 2020;8:83. doi: 10.3389/fbioe.2020.00083. [PubMed: 32266221]. [PubMed Central: PMC7105900].
2. Arjmand B, Goodarzi P, Mohamadi-Jahani F, Falahzadeh K, Larijani B. Personalized Regenerative Medicine. *Acta Med Iran*. 2017;55(3):144-9. [PubMed: 28282715].
3. Atala A. Tissue engineering and regenerative medicine: concepts for clinical application. *Rejuvenation Res*. 2004;7(1):15-31. doi: 10.1089/154916804323105053. [PubMed: 15256042].
4. Mao AS, Mooney DJ. Regenerative medicine: Current therapies and future directions. *Proc Natl Acad Sci U S A*. 2015;112(47):14452-9. doi: 10.1073/pnas.1508520112. [PubMed: 26598661]. [PubMed Central: PMC4664309].
5. Wyles SP, Hayden RE, Meyer FB, Terzic A. Regenerative medicine curriculum for next-generation physicians. *NPJ Regen Med*. 2019;4:3. doi: 10.1038/s41536-019-0065-8. [PubMed: 30774984]. [PubMed Central: PMC6367326].
6. Eltom A, Zhong G, Muhammad A. Scaffold techniques and designs in tissue engineering functions and purposes: A review. Advances in Materials Science and Engineering. 2019;2019.
7. Nerem RM. Tissue engineering in the USA. *Med Biol Eng Comput*. 1992;30(4):CE8-12. doi: 10.1007/BF02446171. [PubMed: 1487936].
8. Howard D, Buttery LD, Shakesheff KM, Roberts SJ. Tissue engineering: strategies, stem cells and scaffolds. *J Anat*. 2008;213(1):66-72. doi: 10.1111/j.1469-7580.2008.00878.x. [PubMed: 18422523]. [PubMed Central: PMC2475566].
9. Murphy CM, O'Brien FJ, Little DG, Schindeler A. Cell-scaffold interactions in the bone tissue engineering triad. *Eur Cell Mater*. 2013;26:120-32. doi: 10.22203/ecm.v026a09. [PubMed: 24052425].
10. Sipe JD. Tissue engineering and reparative medicine. *Ann N Y Acad Sci*. 2002;961:1-9. doi: 10.1111/j.1749-6632.2002.tb03040.x. [PubMed: 12081856].
11. Pereira H, Cengiz F, Silva-Correia J, Oliveira M, Reis RL, Espregueira-Mendes J. Human Meniscus: From biology to tissue engineering strategies. In: Hutson M, Speed C, Editors. Sports injuries. Berlin, Germany: Springer; 2015. p. 1089-102.
12. Tatara AM, Mikos AG. Tissue engineering in orthopaedics. *J Bone Joint Surg Am*. 2016;98(13):1132-9. doi: 10.2106/JBJS.16.00299. [PubMed: 27385687]. [PubMed Central: PMC4928040].
13. Dzobo K, Thomford NE, Senthebane DA, Shipanga H, Rowe A, Dandara C, et al. Advances in regenerative medicine and tissue engineering: innovation and transformation of medicine. *Stem Cells Int*. 2018;2018:2495848. doi: 10.1155/2018/2495848. [PubMed: 30154861]. [PubMed Central: PMC6091336].
14. Bean AC, Huard J. Tissue engineering applications in orthopedic surgery. In: Meyer U, Meyer T, Handschel J, Wiesmann HP, Editors. Fundamentals of tissue engineering and regenerative medicine. Berlin, Germany: Springer Science & Business Media; 2009. p. 913-9.
15. Laurencin CT, Ambrosio AM, Borden MD, Cooper JA Jr. Tissue engineering: orthopedic applications. *Annu Rev Biomed Eng*. 1999;1:19-46. doi: 10.1146/annurev.bioeng.1.1.19. [PubMed: 11701481].
16. Cengiz IF, Pereira H, de GL, Cucchiarini M, Espregueira-Mendes J, Reis RL, et al. Orthopaedic regenerative tissue engineering en route to the holy grail: disequilibrium between the demand and the supply in the operating room. *J Exp Orthop*. 2018;5(1):14. doi: 10.1186/s40634-018-0133-9. [PubMed: 29790042]. [PubMed Central: PMC5964057].
17. Alexander PG, Hofer HR, Clark KL. Mesenchymal stem cells in musculoskeletal tissue engineering. In: Lanza R, Langer R, Vacanti JP, Editors. Principles of tissue engineering. Cambridge, MA: Academic Press; 2014. p. 1171-99.
18. Amini AR, Laurencin CT, Nukavarapu SP. Bone tissue engineering: recent advances and challenges. *Crit Rev Biomed Eng*. 2012;40(5):363-408. doi: 10.1615/critrevbiomedeng.v40.i5.10. [PubMed: 23339648]. [PubMed Central: PMC3766369].
19. Shrivats AR, McDermott MC, Hollinger JO. Bone tissue engineering: state of the union. *Drug Discov Today*. 2014;19(6):781-6. doi: 10.1016/j.drudis.2014.04.010. [PubMed: 24768619].
20. Sheikh Z, Najeeb S, Khurshid Z, Verma V, Rashid H, Glogauer M. Biodegradable Materials for Bone Repair and Tissue Engineering Applications. *Materials (Basel)*. 2015;8(9):5744-94. doi: 10.3390/ma8095273. [PubMed: 28793533]. [PubMed Central: PMC5512653].
21. Travnickova M, Bacakova L. Application of adult mesenchymal stem cells in bone and vascular tissue engineering. *Physiol Res*. 2018;67(6):831-50. doi: 10.33549/physiolres.933820. [PubMed: 30204468].
22. Mishra R, Bishop T, Valerio IL, Fisher JP, Dean D. The potential impact of bone tissue engineering in the clinic. *Regen Med*. 2016;11(6):571-87. doi: 10.2217/rme-2016-0042. [PubMed: 27549369]. [PubMed Central: PMC5007661].
23. Wubneh A, Tsekoura EK, Ayranci C, Uludag H. Current state of fabrication technologies and materials for bone tissue engineering. *Acta Biomater*. 2018;80:1-30. doi: 10.1016/j.actbio.2018.09.031. [PubMed: 30248515].
24. Hernigou P, Poignard A, Zilber S, Rouard H. Cell therapy of hip osteonecrosis with autologous bone marrow grafting. *Indian J Orthop*. 2009;43(1):40-5. doi: 10.4103/0019-5413.45322. [PubMed: 19753178]. [PubMed: PMC2739495].
25. Schmitt A, van Griensven M., Imhoff AB, Buchmann S. Application of stem cells in orthopedics. *Stem Cells Int*. 2012;2012:394962. doi: 10.1155/2012/394962. [PubMed: 22550505]. [PubMed Central: PMC3328166].
26. Goel A, Sangwan SS, Siwach RC, Ali AM. Percutaneous bone marrow grafting for the treatment of tibial non-union. *Injury*. 2005;36(1):203-6. doi: 10.1016/j.injury.2004.01.009. [PubMed: 15589942].
27. Russo S, Sadile F, Esposito R, Mosillo G, Aitanti E, Busco G, et al. Italian experience on use of E.S.W. therapy for avascular necrosis of femoral head. *Int J Surg*. 2015;24(Pt B):188-90. doi: 10.1016/j.ijsu.2015.11.038. [PubMed: 26644278].
28. Miller MA, Ivkovic A, Porter R, Harris MB, Estok DM, Smith RM, et al. Autologous bone grafting on steroids: preliminary clinical results. A novel treatment for nonunions and segmental bone defects. *Int Orthop*. 2011;35(4):599-605. doi:

10.1007/s00264-010-1013-9. [PubMed: 20414656]. [PubMed Central: PMC3066321].
29. Tateiwa D, Yoshikawa H, Kaito T. Cartilage and Bone Destruction in Arthritis: Pathogenesis and Treatment Strategy: A Literature Review. *Cells*. 2019;8(8):818. doi: 10.3390/cells8080818. [PubMed: 31382539]. [PubMed Central: PMC6721572].
30. Vinatier C, Guicheux J. Cartilage tissue engineering: From biomaterials and stem cells to osteoarthritis treatments. *Ann Phys Rehabil Med*. 2016;59(3):139-44. doi: 10.1016/j.rehab.2016.03.002. [PubMed: 27079583].
31. Medvedeva EV, Grebenik EA, Gornostaeva SN, Telpuhov VI, Lychagin AV, Timashev PS, et al. Repair of Damaged Articular Cartilage: Current Approaches and Future Directions. *Int J Mol Sci*. 2018;19(8):2366. doi: 10.3390/ijms19082366. [PubMed: 30103493]. [PubMed Central: PMC6122081].
32. Abdel-Sayed P, Pioletti DP. Strategies for improving the repair of focal cartilage defects. *Nanomedicine (Lond)*. 2015;10(18):2893-905. doi: 10.2217/nnm.15.119. [PubMed: 26377158].
33. Brittberg M, Gomoll AH, Canseco JA, Far J, Lind M, Hui J. Cartilage repair in the degenerative ageing knee. *Acta Orthop*. 2016;87(sup363):26-38. doi: 10.1080/17453674.2016.1265877. [PubMed: 27910738]. [PubMed Central: PMC5389429].
34. Kwon H, Brown WE, Lee CA, Wang D, Paschos N, Hu JC, et al. Surgical and tissue engineering strategies for articular cartilage and meniscus repair. *Nat Rev Rheumatol*. 2019;15(9):550-70. doi: 10.1038/s41584-019-0255-1. [PubMed: 31296933]. [PubMed Central: PMC7192556].
35. Richardson SM, Kalamegam G, Pushparaj PN, Matta C, Memic A, Khademhosseini A, et al. Mesenchymal stem cells in regenerative medicine: Focus on articular cartilage and intervertebral disc regeneration. *Methods*. 2016;99:69-80. doi: 10.1016/j.ymeth.2015.09.015. [PubMed: 26384579].
36. Iwasa J, Engebretsen L, Shima Y, Ochi M. Clinical application of scaffolds for cartilage tissue engineering. *Knee Surg Sports Traumatol Arthrosc*. 2009;17(6):561-77. doi: 10.1007/s00167-008-0663-2. [PubMed: 19020862]. [PubMed Central: PMC2688024].
37. Filardo G, Perdisa F, Roffi A, Marcacci M, Kon E. Stem cells in articular cartilage regeneration. *J Orthop Surg Res*. 2016;11:42. doi: 10.1186/s13018-016-0378-x. [PubMed: 27072345]. [PubMed Central: PMC4830073].
38. Chang YH, Liu HW, Wu KC, Ding DC. Mesenchymal Stem Cells and Their Clinical Applications in Osteoarthritis. *Cell Transplant*. 2016;25(5):937-50. doi: 10.3727/096368915X690288. [PubMed: 26688464].
39. Vega A, Martin-Ferrero MA, Del CF, Alberca M, Garcia V, Munar A, et al. Treatment of Knee Osteoarthritis with Allogeneic Bone Marrow Mesenchymal Stem Cells: A Randomized Controlled Trial. *Transplantation*. 2015;99(8):1681-90. doi: 10.1097/TP.0000000000000678. [PubMed: 25822648].
40. Kim HS, Sun X, Lee JH, Kim HW, Fu X, Leong KW. Advanced drug delivery systems and artificial skin grafts for skin wound healing. *Adv Drug Deliv Rev*. 2019;146:209-39. doi: 10.1016/j.addr.2018.12.014. [PubMed: 30605737].
41. Vig K, Chaudhari A, Tripathi S, Dixit S, Sahu R, Pillai S, et al. Advances in Skin Regeneration Using Tissue Engineering. *Int J Mol Sci*. 2017;18(4):789. doi: 10.3390/ijms18040789. [PubMed: 28387714]. [PubMed Central: PMC5412373].
42. Sheikholeslam M, Wright MEE, Jeschke MG, Amini-Nik S. Biomaterials for Skin Substitutes. *Adv Healthc Mater*. 2018;7(5). doi: 10.1002/adhm.201700897. [PubMed: 29271580].
43. Chouhan D, Dey N, Bhardwaj N, Mandal BB. Emerging and innovative approaches for wound healing and skin regeneration: Current status and advances. *Biomaterials*. 2019;216:119267. doi: 10.1016/j.biomaterials.2019.119267. [PubMed: 31247480].
44. Kaur A, Midha S, Giri S, Mohanty S. Functional Skin Grafts: Where Biomaterials Meet Stem Cells. *Stem Cells Int*. 2019;2019:1286054. doi: 10.1155/2019/1286054. [PubMed: 31354835]. [PubMed Central: PMC6636521].
45. Goodarzi P, Falahzadeh K, Nematizadeh M, Farazandeh P, Payab M, Larijani B, et al. Tissue Engineered Skin Substitutes. *Adv Exp Med Biol*. 2018;1107:143-88. doi: 10.1007/5584_2018_226. [PubMed: 29855826].
46. Rheinwald JG, Green H. Serial cultivation of strains of human epidermal keratinocytes: the formation of keratinizing colonies from single cells. *Cell*. 1975;6(3):331-43. doi: 10.1016/s0092-8674(75)80001-8. [PubMed: 1052771].
47. Chang DK, Louis MR, Gimenez A, Reece EM. The Basics of Integra Dermal Regeneration Template and its Expanding Clinical Applications. *Semin Plast Surg*. 2019;33(3):185-9. doi: 10.1055/s-0039-1693401. [PubMed: 31384234]. [PubMed Central: PMC6680073].
48. Liu Y, Panayi AC, Bayer LR, Orgill DP. Current Available Cellular and Tissue-Based Products for Treatment of Skin Defects. *Adv Skin Wound Care*. 2019;32(1):19-25. doi: 10.1097/01.ASW.0000547412.54135.b7. [PubMed: 30570555].
49. Momeni M, Fallah N, Bajouri A, Bagheri T, Orouji Z, Pahlevanpour P, et al. A randomized, double-blind, phase I clinical trial of fetal cell-based skin substitutes on healing of donor sites in burn patients. *Burns*. 2019;45(4):914-22. doi: 10.1016/j.burns.2018.10.016. [PubMed: 30559055].
50. Vijayavenkataraman S. Nerve guide conduits for peripheral nerve injury repair: A review on design, materials and fabrication methods. *Acta Biomater*. 2020;106:54-69. doi: 10.1016/j.actbio.2020.02.003. [PubMed: 32044456].
51. Jahromi M, Razavi S, Bakhtiari A. The advances in nerve tissue engineering: From fabrication of nerve conduit to in vivo nerve regeneration assays. *J Tissue Eng Regen Med*. 2019;13(11):2077-100. doi: 10.1002/term.2945. [PubMed: 31350868].
52. Gu X, Ding F, Williams DF. Neural tissue engineering options for peripheral nerve regeneration. *Biomaterials*. 2014;35(24):6143-56. doi: 10.1016/j.biomaterials.2014.04.064. [PubMed: 24818883].
53. Belanger K, Dinis TM, Taourirt S, Vidal G, Kaplan DL, Egles C. Recent Strategies in Tissue Engineering for Guided Peripheral Nerve Regeneration. *Macromol Biosci*. 2016;16(4):472-81. doi: 10.1002/mabi.201500367. [PubMed: 26748820].
54. Hussain G, Wang J, Rasul A, Anwar H, Qasim M, Zafar S, et al. Current Status of Therapeutic Approaches against Peripheral Nerve Injuries: A Detailed Story from Injury to Recovery. *Int J Biol Sci*. 2020;16(1):116-34. doi: 10.7150/ijbs.35653. [PubMed: 31892850]. [PubMed Central: PMC6930373].
55. Zhang BG, Quigley AF, Myers DE, Wallace GG, Kapsa RM, Choong PF. Recent advances in nerve tissue engineering. *Int J Artif Organs*. 2014;37(4):277-91. doi: 10.5301/ijao.5000317. [PubMed: 24811182].
56. Kuffler DP, Foy C. Restoration of Neurological Function Following Peripheral Nerve Trauma. *Int J Mol Sci*. 2020;21(5):1808. doi: 10.3390/ijms21051808. [PubMed: 32155716]. [PubMed Central: PMC7084579].
57. Kim JY, Jeon WJ, Kim DH, Rhyu IJ, Kim YH, Youn I, et al. An inside-out vein graft filled with platelet-rich plasma for repair of a short sciatic nerve defect in rats. *Neural Regen Res*. 2014;9(14):1351-7. doi: 10.4103/1673-5374.137587. [PubMed: 25221591]. [PubMed Central: PMC4160865].
58. Roque JS, Pomini KT, Buchaim RL, Buchaim DV, Andreo JC, Roque DD, et al. Inside-out and standard vein grafts associated with platelet-rich plasma (PRP) in sciatic nerve repair. A histomorphometric study. *Acta Cir Bras*. 2017;32(8):617-25. doi: 10.1590/s0102-865020170080000003. [PubMed: 28902937].
59. Sabongi RG, Fernandes M, Dos Santos JB. Peripheral nerve regeneration with conduits: use of vein tubes. *Neural Regen Res*. 2015;10(4):529-33. doi: 10.4103/1673-5374.155428. [PubMed: 26170802]. [PubMed Central: PMC4424734].
60. Boeckstyns ME, Sorensen AI, Vineta JF, Rosen B, Navarro X, Archibald SJ, et al. Collagen conduit versus microsurgical

neurorrhaphy: 2-year follow-up of a prospective, blinded clinical and electrophysiological multicenter randomized, controlled trial. *J Hand Surg Am.* 2013;38(12):2405-11. doi: 10.1016/j.jhsa.2013.09.038. [PubMed: 24200027].
61. Hou Y, Wang X, Zhang Z, Luo J, Cai Z, Wang Y, et al. Repairing Transected Peripheral Nerve Using a Biomimetic Nerve Guidance Conduit Containing Intraluminal Sponge Fillers. *Adv Healthc Mater.* 2019;8(21):e1900913. doi: 10.1002/adhm.201900913. [PubMed: 31583854].
62. Liu J, Saul D, Boker KO, Ernst J, Lehman W, Schilling AF. Current Methods for Skeletal Muscle Tissue Repair and Regeneration. *Biomed Res Int.* 2018;2018:1984879. doi: 10.1155/2018/1984879. [PubMed: 29850487]. [PubMed Central: PMC5926523].
63. Nakayama KH, Shayan M, Huang NF. Engineering Biomimetic Materials for Skeletal Muscle Repair and Regeneration. *Adv Healthc Mater.* 2019;8(5):e1801168. doi: 10.1002/adhm.201801168. [PubMed: 30725530]. [PubMed Central: PMC6589032].
64. Juhas M, Ye J, Bursac N. Design, evaluation, and application of engineered skeletal muscle. *Methods.* 2016;99:81-90. doi: 10.1016/j.ymeth.2015.10.002. [PubMed: 26455485]. [PubMed Central: PMC4821818].
65. An Y, Li D. Engineering skeletal muscle tissue in bioreactor systems. *Chin Med J (Engl).* 2014;127(23):4130-9. [PubMed: 25430462].
66. Passipieri JA, Christ GJ. The Potential of Combination Therapeutics for More Complete Repair of Volumetric Muscle Loss Injuries: The Role of Exogenous Growth Factors and/or Progenitor Cells in Implantable Skeletal Muscle Tissue Engineering Technologies. *Cells Tissues Organs.* 2016;202(3-4):202-13. doi: 10.1159/000447323. [PubMed: 27825153].
67. Cesare G. 10-Muscle tissue engineering. In: Nukavarapu S, Freeman J, Laurencin C, Editors. Regenerative engineering of musculoskeletal tissues and interfaces. Philadelphia, PA: Elsevier Science; 2015. doi: 10.1016/B978-1-78242-301-0.00010-0.
68. Salmaninejad A, Valilou SF, Bayat H, Ebadi N, Daraei A, Yousefi M, et al. Duchenne muscular dystrophy: an updated review of common available therapies. *Int J Neurosci.* 2018;128(9):854-64. doi: 10.1080/00207454.2018.1430694. [PubMed: 29351004].
69. Langer R, Vacanti JP. Tissue engineering. *Science.* 1993;260(5110):920-6. doi: 10.1126/science.8493529. [PubMed: 8493529].
70. Gilbert-Honick J, Grayson W. Vascularized and Innervated Skeletal Muscle Tissue Engineering. *Adv Healthc Mater.* 2020; 9(1):e1900626. doi: 10.1002/adhm.201900626. [PubMed: 31622051]. [PubMed Central: PMC6986325].
71. Mase VJ Jr, Hsu JR, Wolf SE, Wenke JC, Baer DG, Owens J, et al. Clinical application of an acellular biologic scaffold for surgical repair of a large, traumatic quadriceps femoris muscle defect. *Orthopedics.* 2010;33(7):511. doi: 10.3928/01477447-20100526-24. [PubMed: 20608620].
72. Wang HD, Lough DM, Kurlander DE, Lopez J, Quan A, Kumar AR. Muscle-derived stem cell-enriched scaffolds are capable of enhanced healing of a murine volumetric muscle loss defect. *Plast Reconstr Surg.* 2019;143(2):329e-39e. doi: 10.1097/PRS.0000000000005273. [PubMed: 30531618].
73. Dong C, Lv Y. Application of Collagen Scaffold in Tissue Engineering: Recent Advances and New Perspectives. *Polymers (Basel).* 2016;8(2):42. doi: 10.3390/polym8020042. [PubMed: 30979136]. [PubMed Central: PMC6432532].
74. Mace J, Wheelton A, Khan WS, Anand S. The Role of Bioreactors in Ligament and Tendon Tissue Engineering. *Curr Stem Cell Res Ther.* 2016;11(1):35-40. doi: 10.2174/1574888x10666150904113827. [PubMed: 26337379].
75. Lim WL, Liau LL, Ng MH, Chowdhury SR, Law JX. Current Progress in Tendon and Ligament Tissue Engineering. *Tissue Eng Regen Med.* 2019;16(6):549-71. doi: 10.1007/s13770-019-00196-w. [PubMed: 31824819]. [PubMed Central: PMC6879704].
76. Snedeker JG, Foolen J. Tendon injury and repair - A perspective on the basic mechanisms of tendon disease and future clinical therapy. *Acta Biomater.* 2017;63:18-36. doi: 10.1016/j.actbio.2017.08.032. [PubMed: 28867648].
77. Qazi TH, Duda GN, Ort MJ, Perka C, Geissler S, Winkler T. Cell therapy to improve regeneration of skeletal muscle injuries. *J Cachexia Sarcopenia Muscle.* 2019;10(3):501-16. doi: 10.1002/jcsm.12416. [PubMed: 30843380]. [PubMed Central: PMC6596399].
78. Wang A, Breidahl W, Mackie KE, Lin Z, Qin A, Chen J, et al. Autologous tenocyte injection for the treatment of severe, chronic resistant lateral epicondylitis: A pilot study. *Am J Sports Med.* 2013;41(12):2925-32. doi: 10.1177/0363546513504285. [PubMed: 24068695].
79. Pearlin, Nayak S, Manivasagam G, Sen D. Progress of regenerative therapy in orthopedics. Curr *Osteoporos Rep.* 2018;16(2):169-81. doi: 10.1007/s11914-018-0428-x. [PubMed: 29488062].
80. Oreffo RO, Triffitt JT. Future potentials for using osteogenic stem cells and biomaterials in orthopedics. *Bone* 1999; 25(2 Suppl): 5S-9S. doi: 10.1016/s8756-3282(99)00124-6. [PubMed: 10458266].
81. Berebichez-Fridman R, Montero-Olvera PR. Sources and clinical applications of mesenchymal stem cells: State-of-the-art review. *Sultan Qaboos Univ Med J.* 2018;18(3):e264-e277. doi: 10.18295/squmj.2018.18.03.002. [PubMed: 30607265]. [PubMed Central: PMC6307657].
82. Tang D, Tare RS, Yang LY, Williams DF, Ou KL, Oreffo RO. Biofabrication of bone tissue: Approaches, challenges and translation for bone regeneration. *Biomaterials.* 2016;83: 363-82. doi: 10.1016/j.biomaterials.2016.01.024. [PubMed: 26803405].
83. Zhang W, Zhu Y, Li J, Guo Q, Peng J, Liu S, et al. Cell-derived extracellular matrix: Basic characteristics and current applications in orthopedic tissue engineering. *Tissue Eng Part B Rev.* 2016;22(3):193-207. doi: 10.1089/ten.TEB.2015.0290. [PubMed: 26671674].
84. Phull AR, Eo SH, Abbas Q, Ahmed M, Kim SJ. Applications of Chondrocyte-Based Cartilage Engineering: An Overview. *Biomed Res Int.* 2016;2016:1879837. doi: 10.1155/2016/1879837. [PubMed: 27631002]. [PubMed Central: PMC5007317].
85. Rai V, Dilisio MF, Dietz NE, Agrawal DK. Recent strategies in cartilage repair: A systemic review of the scaffold development and tissue engineering. *J Biomed Mater Res A.* 2017;105(8):2343-54. doi: 10.1002/jbm.a.36087. [PubMed: 28387995].
86. Ho J, Walsh C, Yue D, Dardik A, Cheema U. Current Advancements and Strategies in Tissue Engineering for Wound Healing: A Comprehensive Review. *Adv Wound Care (New Rochelle).* 2017;6(6):191-209. doi: 10.1089/wound.2016.0723. [PubMed: 28616360]. [PubMed Central: PMC5467128].
87. Zhou H, You C, Wang X, Jin R, Wu P, Li Q, et al. The progress and challenges for dermal regeneration in tissue engineering. *J Biomed Mater Res A.* 2017;105(4):1208-18. doi: 10.1002/jbm.a.35996. [PubMed: 28063210].
88. Talikowska M, Fu X, Lisak G. Application of conducting polymers to wound care and skin tissue engineering: A review. *Biosens Bioelectron.* 2019;135:50-63. doi: 10.1016/j.bios.2019.04.001. [PubMed: 30999241].
89. Ng WL, Yeong WY, Naing MW. Cellular approaches to tissue-engineering of skin: A Review. *J Tissue Sci Eng.* 2015;6(2):1000150. doi: 10.4172/2157-7552.1000150.
90. Han YF, Tao R, Sun TJ, Chai JK, Xu G, Liu J. Advances and opportunities for stem cell research in skin tissue engineering. *Eur Rev Med Pharmacol Sci.* 2012;16(13):1873-7. [PubMed: 23208974].
91. Nourian Dehkordi A, Mirahmadi Babaheydari F, Chehelgerdi M, Raeisi Dehkordi S. Skin tissue engineering: Wound healing based on stem-cell-based therapeutic strategies. *Stem Cell Res Ther.* 2019;10(1):111. doi: 10.1186/s13287-019-1212-2. [PubMed: 30922387]. [PubMed Central: PMC6440165].

92. Li R, Li DH, Zhang HY, Wang J, Li XK, Xiao J. Growth factors-based therapeutic strategies and their underlying signaling mechanisms for peripheral nerve regeneration. *Acta Pharmacol Sin*. 2020;41(10):1289-300. doi: 10.1038/s41401-019-0338-1. [PubMed: 32123299].
93. Hoffmann A, Gross G. Tendon and ligament engineering: from cell biology to in vivo application. *Regen Med*. 2006;1(4):563-74. doi: 10.2217/17460751.1.4.563. [PubMed: 17465850].
94. Sharma P, Kumar P, Sharma R, Bhatt VD, Dhot PS. Tissue engineering; current status & futuristic Scope. *J Med Life*. 2019;12(3):225-9. doi: 10.25122/jml-2019-0032. [PubMed: 31666821]. [PubMed Central: PMC6814873].
95. Griffith LG, Naughton G. Tissue engineering–current challenges and expanding opportunities. *Science*. 2002;295(5557):1009-14. doi: 10.1126/science.1069210. [PubMed: 11834815].
96. Usas A, Maciulaitis J, Maciulaitis R, Jakuboniene N, Milasius A, Huard J. Skeletal muscle-derived stem cells: implications for cell-mediated therapies. *Medicina (Kaunas)*. 2011;47(9):469-79. [PubMed: 22156603].
97. Pang C, Ibrahim A, Bulstrode NW, Ferretti P. An overview of the therapeutic potential of regenerative medicine in cutaneous wound healing. *Int Wound J*. 2017;14(3):450-9. doi: 10.1111/iwj.12735. [PubMed: 28261962].
98. Grounds MD. Obstacles and challenges for tissue engineering and regenerative medicine: Australian nuances. *Clin Exp Pharmacol Physiol*. 2018;45(4):390-400. doi: 10.1111/1440-1681.12899. [PubMed: 29193254].
99. Pina S, Ribeiro VP, Marques CF, Maia FR, Silva TH, Reis RL, et al. Scaffolding Strategies for Tissue Engineering and Regenerative Medicine Applications. *Materials (Basel)*. 2019;12(11):1824. doi: 10.3390/ma12111824. [PubMed: 31195642]. [PubMed Central: PMC6600968].